III. REMARKS

The undersigned gratefully acknowledges the courtesies extended by Examiners Gollamudi and Hartley during the interview conducted on November 20, 2003.

A. Pending Claims

Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and independent claims 76-81 are pending. Claims 21-22 and 25-26 have been amended in order to correct the dependencies of the claims.

B. Rejections Under 35 U.S.C. § 103

During the interview conducted on November 20, 2003, it was pointed out to the Examiners that the rejections made in the last Office Action were based in part on misinterpretations of the data presented in the Cheng, et al. reference, and it was respectfully submitted that the combinations relied upon by the Examiner were not proper in that the stated motivation to combine was misplaced, and that the Examiner only arrived at the combinations through the improper use of hindsight to arrive at the subject matter of the pending claims.

In the Office Action dated October 20, 2003, the Examiner finally rejected claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71, and 76-81 under 35 U.S.C. 103 (a) as being unpatentable over Alberts (4,997,658) or Cheng et al (Pharmaceutical Research) in view of Oshlack et al. (5,472,712).

This rejection is respectfully traversed. It is respectfully submitted that (i) the Examiner has misinterpreted the Cheng, et al. reference, and therefore has misapplied it; (ii) that the alleged motivation that the Examiner has provided for combining the Alberts or Cheng, et al.

references with Oshlack et al. is incorrect and fails in view of the above-stated standards for finding motivation to combine references, and the Examiner is improperly using a hindsight analysis to arrive at the motivation to combine; (iii) even if one were to combine the references in the manner stated by the Examiner in the last office action, one would not arrive at the claimed invention; among other things.

As explained during the Interview conducted on November 20, 2003, the Examiner has made statements in the last Office Action which demonstrate that the Examiner has misunderstood the meaning of the T_{max} parameter, which in turn led the Examiner to make incorrect conclusions regarding obviousness.

As previously explained (i) during the Interview conducted on June 27, 2003; (ii) in applicants' last Amendment dated July 22, 2003; and (iii) during the Interview conducted on November 20, 2003, one cannot determine a T_{max} from a plasma concentration curve. The T_{max} parameter is a numerical value determined from the time that the maximum (measured) drug plasma concentration (C_{max}) is reached in a patient, whenever that occurs during the dosing interval (and a mean Tmax is the average of the Tmax values for all patients, e.g., in a particular study). On the other hand, the plasma concentration curve for a single patient is a plot of the concentration of drug in the blood at each tested time point during the dosing interval. A mean plasma concentration curve provides the average plasma concentration of drug for all patients at each tested time point. The T_{max} and C_{max} values are nowhere to be found on a mean plasma concentration curve.

Nevertheless, the Examiner in the last office action stated the following with respect to Cheng et al. – "The instant Cmax is taught (figures)". (Page 3, line 7 and page 4, last line, in the last Office Action).

During the Interview, the undersigned went through the Cheng et al. reference with the Examiners page by page, and demonstrated that the figures 1 and 2 contained therein were directed to in-vitro dissolution testing, and while that figures 3-5 showed in-vivo testing in dogs or humans, these figures did not provide T_{max} data. Rather, it was pointed out that the plasma curves for the tested controlled release (CRS8, CRS14, MODS8, MODS12 and MODS14) and sustained release (SRT8 and SRT14) read in conjunction with the corresponding data concerning those formulations in Tables II and III showed that (i) all of these formulations were not bioavailable compared to the reference standard (the immediate release formulation, CT), and that the only bioavailable formulation, SRT14, had a T_{max} of 2.3 hours. It was pointed out that none of the T_{max} data in Cheng et al. was suggestive of the T_{max} range set forth in the pending claims.

In the last Office Action, the Examiner indicated that "the applicant needs to address the assertion of the difference between dog data and human data". By this, the Examiner apparently desired the presentation of experimental data. As explained during the Interview, no such data is needed. This apparent "requirement" was based on the statement in the Amendment dated July 22, 2003 wherein it was noted that the Cheng et al. reference states that the dog may not be a good model for predicting relative bioavailability in humans. This statement was only made in *furtherance* of applicants' arguments, and only *after* it was pointed out that none of the formulations provided the T_{max} range set forth in the pending claims.

The Cheng et al. reference speaks for itself. It provides in vivo experimental data which is not indicative of the claimed formulations and methods. On the other hand, the exemplified formulations of the present invention provide abundant amounts of in vivo data supporting the claims. In the last Office Action, the Examiner also indicated that if "applicant contends there is a marked difference between the prior art's release and the instant invention's, then applicant must provide evidence in a Rule 132 Declaration." Once again, as explained during the

Interview conducted on November 22, 2003, this evidence was provided in the specification of the application.

During the Interview, the Examiner apparently conceded that Cheng et al. does not teach the T_{max} range set forth in the pending claims, but that the Examiner was instead relying on Oshlack et al. for teaching the same.

The Examiner's reliance on the combination of Cheng et al. and Oshlack is respectfully traversed. It is respectfully submitted that there is no motivation whatsoever to combine these references in the manner suggested by the Examiner. The Examiner is reminded that Cheng et al. describes in vitro and in vivo testing of controlled and sustained release matrix formulations, and controlled release coated tablets containing lovastatin or simvastatin. Oshlack et al. describe the preparation of *stabilized* controlled release coatings. To the extent that Oshlack et al. mention T_{max}, it is *only* with respect to certain exemplified formulations set forth therein (in Tables 51 and 52) concerning a *single drug (morphine) unrelated to the class of alkyl esters of hydroxyl substituted naphthalenes.* There is no generalized statement in Oshlack et al. relating to T_{max}, and there is no suggestion whatsoever in Oshlack et al. that the Tmax achieved in the examples set forth in Tables 51 and 52 would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxyl substituted naphthalenes.

However, even assuming arguendo that the Examiner could somehow justify the combination of Cheng et al. and Oshlack et al., it is respectfully submitted there is no suggestion of the the T_{max} range set forth in the pending claims. Oshlack et al. in Tables 51 and 52 do not demonstrate any T_{max} in that range. As mentioned during the Interview conducted on November 20, 2003, the Examiner's comment on page 7, lines 17-19 that Oshlack "teaches a Tmax of 9" in figure 16 is respectfully submitted to be simply incorrect. Figure 16 does not provide any information about T_{max}. The Examiner's statement in the Office Action alleging that "standard

deviation would have the Tmax fall within the recited range" is baseless. There simply is no standard deviation information provided with respect to Example 23, with respect to T_{max} or any other pharmacokinetic value. Therefore, it is respectfully submitted that the Examiner's combination fails to suggest the claimed invention.

During the interview, the undersigned directed the Examiners' attention to the language of *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), which states the following concerning whether there is a teaching, motivation, or suggestion to select and combine references relied on as evidence of obviousness:

> "The factual inquiry whether to combine references must be thorough and searching." *ID.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art refereces is an 'essential component of an obviousness holding' ") (quoting *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5USPQ2d 1596, 1600 (Fed. Cir. 1988) (" 'teachings of references can be combined *only* if there is some suggestion or incentive to do so.' ") (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).

During the Interview conducted on November 20, 2003, it is respectfully submitted that the Examiner relied on a hindsight analysis to support the rejections based on obviousness. Furthermore, it was strongly urged by the undersigned that the Examiner could not properly pick a T_{max} "out of a hat" and combine it with Cheng et al. to arrive at the claimed invention without

providing the clear motivation to do so. The Examiner is reminded that Cheng et al. provide methods and formulations which have demonstrated T_{max} data, which are not within the pending claims. As argued during the Interview conducted on November 20, 2003, it is respectfully submitted that a reference citing a later T_{max} than that set forth in Cheng et al. *for a different class of drugs* does not provide the motivation to modify Cheng et al. to arrive at the presently claimed invention.

As previously discussed in the Amendment dated July 22, 2003, Alberts et al. concerns a method of administering an HMG-CoA Reductase Inhibitor utilizing a drug-delivery device for the controlled release of the drug into an environment of use. (See, column 2, lines 55-58). Alberts et al state that "[u]tilizing controlled or sustained release technologies, a single administration of the indicated daily dosage amount delivers drug over an extended period of time (i.e. 6 to 24 hours)." Column 1, lines 39-44). There is absolutely no information contained in Alberts et al. concerning the T_{max} parameter. The only information in Alberts et al. directed to the in-vivo performance of its formulations is found at Example 2, columns 5-6, wherein the controlled-release preparation afforded controlled in-vitro release of the drug over a 6-10 hour period. (See, column 5, lines 63-66).

It is respectfully submitted that the Examiner has provided no plausible motivation to combine Alberts et al. with Oshlack et al. To the extent that Alberts et al. mention controlled or sustained release technology, the technologies described therein do not appear to based on the types of aqueous based controlled release coatings that are the subject of the Oshlack et al. invention. Even assuming arguendo that these references are properly combinable, the Examiner's basis for reliance on the Oshlack et al. reference (T_{max}) is respectfully submitted to be misplaced as Oshlack et al. do not report such a value within the claims, nor do they report any work on the class of drugs included in the presently claimed formulations, among many other things.

In the Office Action dated October 20, 2003, the Examiner further rejected claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71, and 76-81 under 35 U.S.C. 103 (a) as being unpatentable over Alberts (4,997,658) or Cheng et al (Pharmaceutical Research) in view of Sako et al. (6,436,441).

As discussed during the Interview conducted on November 20, 2003, it is respectfully submitted that the Sako et al. reference adds no information which is related to the T_{max} parameter, and therefore even if properly combinable with either Alberts et al. or Cheng et al., does not render the claimed invention obvious. As previously discussed in the Amendment dated July 22, 2003, the Sako et al. reference is directed to hydrogel-type sustained-release preparations which provides release in the colon, as well as the upper portion of the gastrointestinal tract. None of the exemplified formulations includes a drug that is a HMG-CoA Reductase Inhibitor, and no information is provided in this reference concerning generalized or desired time to maximum plasma concentration for any drug, let alone a HMG-CoA Reductase Inhibitor. Sako et al. is apparently relied on solely because it mentions a hyperlipemia treating agent among a long list of unrelated drugs to which the therein described technology might be applied.

To the extent that the Examiner apparently relies on Sako et al. for the proposition that controlled or sustained release formulations can be manipulated to achieve various results, the Examiner neglects to provide any basis whatsoever that the combination of Sako et al. with either Alberts et al. or Cheng et al. would lead to the claimed invention. The Examiner only reaches this conclusion through the improper use of hindsight. To the extent that Sako is relied upon in the stated manner, it is not properly combinable with either Alberts et al. or Cheng et al. because it adds nothing.

IV. Conclusion

It is now believed that the above-referenced rejections have been obviated and withdrawal is respectfully requested. It is believed that all claims are now in condition for allowance.

The Examiner is urged to contact the undersigned by telephone if any issues remain to be resolved.

An early and favorable action is earnestly solicited.

Respectfully submitted,
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